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RESEARCH ARTICLE

EVALUATION OF THE POTENTIAL EFFECT OF CURCUMIN AND/OR PARACETAMOL IN PREGNANT WISTAR RATS AND THEIR FETUSES

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ABSTRACT

The present study aimed to assess the potential effects of curcumin and/or paracetamol on maternal Wistar rats (*Rattus norvegicus*) and their fetuses during gestation. The pregnant female Wistar rats were allotted into four groups (6 rats/each group): the control group received daily/orally vehicle, curcumin (15.75 mg/kg body weight) group, paracetamol (350 mg/kg body weight) group, and the combined group received paracetamol and curcumin simultaneously during gestation (6^{th}–19^{th} days). This study measured pregnancy outcome parameters, fetal skeletal status, hepatic oxidative stress, and histological changes. The current results revealed the unsafe consequence of paracetamol on the pregnancy outcome. At the same time, it induced fetal growth retardation, hepatic histological alterations, and altered significantly (P<0.05) the maternal and fetal hepatic oxidative status. Paracetamol intake did not affect skeletal bone ossification. On the contrary, curcumin daily intake alleviated the negative impact of paracetamol and improved fetal growth parameters, restored the normal hepatic histology, decreased lipid peroxidation levels, and increased antioxidants in maternal and fetal liver tissues. In conclusion, curcumin could be approved as a protective agent that reverses the toxic effect of paracetamol during gestation. Further studies will be done to illustrate the precise mechanisms and pathways by which the curcumin can alleviate the paracetamol impact.

INTRODUCTION

Paracetamol is one of the most effective analgesics and antipyretic medications in use today. It is a synthetic, non-opioid, amino-phenol-derived medication that is used by millions of patients worldwide, notably in specific populations like children, the elderly, and pregnant women[1,2]. It is also the only drug not requiring a prescription due to its safety during pregnancy. However, a more cautious approach would be necessary given that some studies reveal behavioral impacts in the offspring of dams that received paracetamol during gestation[2]. The placental barrier is breached by para-cetamol due to its low molecular weight[3], allowing around 40% of the drug's levels in the mother's bloodstream to reach the developing fetuses[4]. Hepatotoxicity in both the mother and the fetus can result from paracetamol overdoses that cross the placenta[5]. It also changes the renal structure during pregnancy in Sprague Dawley rats[6]. One of the main causes of acute renal

failure is acute tubular necrosis caused by paracetamol[7]. Paracetamol can also cause oxidative stress changes *via* increasing malondialdehyde (MDA) and decreasing reduced glutathione (GSH) and superoxide dismutase (SOD) in rats[8].

Extensive research has been conducted on curcumin due to its diverse array of characteristics, encompassing antioxidant, anti-inflammatory, immunomodulatory, anti-toxicant, antiapoptotic, neuroprotective, hepatoprotective, antiangiogenic, antihypertensive, and antidiabetic activities[9,10]. Consequently, curcumin is currently regarded as an exciting treatment option for many illnesses[11,12]. According to animal and *in vitro* research findings, curcumin exhibits potential utility in mitigating the adverse programming processes that transpire throughout gestation such as gestational diabetic mellitus, preeclampsia characterized by elevated blood pressure, obstetrical growth problems, and the detrimental effects caused by toxic substances and environmental factors[13,14]. Furthermore, the promising results derived from preclinical investigations regarding the utilization of curcumin in various neurological disorders[15] indicate a potential therapeutic application in the treatment of post-partum depression, a commonly overlooked ailment related to pregnancy[16]. The current investigation aimed to determine the potential ameliorative effects of curcumin against paracetamol-induced oxidative stress and histological alterations during pregnancy.

MATERIAL AND METHODS

Ethical standards

The Institutional Animal Care and Use Committee (IACUC) of Cairo University, Faculty of Science (Egypt) granted clearance to all experimental protocols and procedures utilized in this study under approval number: CU/I/F/4/21.

Drug and natural product

Paracetamol tablets (500 mg/tablet) were purchased from a local pharmacy, Egypt. Curcumin powder (purity: 95%, molecular formula: $C_{21}H_{20}O_6$, molecular weight: 368.39 g/mol, CSA: 458-37-7), the active ingredient of turmeric, was purchased from Fisher Scientific (Hampton, NH, USA).

Animal housing

Adult male and female rats of the Wistar strain (*Rattus norvegicus*) were acquired from the animal facility at the Faculty of Veterinary, Cairo University. The rats exhibited an average age of around 2 to 2.5 months, with a corresponding weight range of 170-180 g. By standard environmental conditions, including a temperature range of 25±2ºC, humidity levels of 60±20%, and a light/dark cycle of 12 hours each, the female rats in their pre-mating stage were paired with male rats (two females per male) for the duration of an overnight session. The detection of spermatozoa in the vaginal smear was a dependable marker for determining the initial gestation day.

Experimental procedure and dosage

A total of 24 gravid rats were allotted into four distinct groups for this study. The initial control group was administered orally and daily with distilled water (vehicle of paracetamol) and maize oil (vehicle of curcumin); the other three experimental cohorts, six rats/each group, were subjected to different therapies orally and daily during gestation period (6^{th}–19^{th} days). One the treated group was administered a daily dose of 15.75 mg/kg of curcumin, as documented by Badawy *et al.*[17]. The second treated group received a dosage of 350 mg/kg of paracetamol, as Aleixo *et al.*[18] reported**.** The third treated group was subjected to the simultaneous administration of curcumin and paracetamol.

Growth observations

The weights of all gravid rats were determined, and their uteri were weighed before dissection on the 20^{th} day of gestation. The evaluation encompassed the quantification of fetal weight and length and

the measurement of placental weight. The weights of the dams were measured at the beginning and end of their pregnancy periods.

Reproductive measurements

The quantification of corpora lutea in both the right and left ovaries was performed in both the control and treatment groups. The researchers tracked the number of implantations, both viable and non-viable fetuses. The pre-and postimplantation loss index was measured following the methodology outlined by Burdan *et al.*[19]. The formula for calculating preimplantation loss as a percentage is derived by dividing the difference between the number of corpora lutea and the number of implantation sites by the number of corpora lutea and then multiplying the result by 100. The formula for calculating postimplantation loss as a percentage is derived by subtracting the number of live fetuses from the number of implantation sites, dividing this difference by the number of implantation sites, and then multiplying the result by 100.

Fetal skeletal examination

Fetuses were kept in 95% ethyl alcohol for dehydration and prepared for staining with Alcian blue (for cartilage) and Alizarin red (for bone) according to the method described by Young *et al*.[20].

Oxidative stress and antioxidant status investigation

To examine oxidative stress, tissues from both the maternal and fetal liver were segregated into distinct groups and afterwards preserved at a temperature of –20°C. The tissue samples were divided into smaller portions and homogenized in a solution with a pH of 7.4, using a concentration of 10 mmol/L of phosphate buffer saline (PBS). The homogenates underwent centrifugation, and the resulting supernatants were utilized for the colorimetric determination of reduced glutathione (GSH, catalogue number: GR2511), catalase (CAT, catalogue number: CA2517), superoxide dismutase (SOD, catalogue number: SD2521), and malondialdehyde (MDA, catalogue number: MD2529) using kits manufactured by BioDiagnostic (Giza Governorate, Egypt).

Histological analysis

The liver tissues from the mother and fetus were preserved using a solution of 10% neutral buffered formalin. These tissues were then cut into sections and stained with hematoxylin and eosin, a common method used for routine evaluation[21]. The quantitative examination of liver histology in maternal and fetal specimens was assessed following the methodology outlined by Majeed *et al*.[22]. The Leica QWin DW3000 image analysis system (Cambridge, England) was utilized to evaluate the number of degraded hepatocytes, inflammatory cell infiltrations, and the extent of congestion per cross-sectional area in hepatic tissue.

Statistical analysis

Our data were reported as means ± standard errors. One-way analysis of variance was performed using the social science statistical software (SPSS), version 10.0 for Windows. The statistical differences among the experimental groups were demonstrated using the least significant difference (LSD) test.

RESULTS

Effect of curcumin and paracetamol on the body and reproductive organs weights in rats

According to the data shown in Table "1", a significant reduction ($P<0.05$) in the body weight gain was observed in the paracetamol group compared with the control group. Dams subjected to curcumin treatment exhibited no statistically significant alterations ($P\geq0.05$) compared with the control group. The concurrent administration of paracetamol+curcumin demonstrated significant ($P<0.05$) reduction and rise in the body weight gain compared with the control group and the paracetamol

group, respectively. There was no reported significant alteration ($P \geq 0.05$) in the weights of the uterus or placenta among the groups participating in the study.

Effect of curcumin and paracetamol on the morphological characterizations of rats' fetuses

In each of the three experimental groups, the occurrence of resorption sites or deceased fetuses' numbers did not found, and no statistically significant alteration ($P \geq 0.05$) was observed in the post-implantation loss index. The experimental group of rats subjected to paracetamol and paracetamol+ curcumin exhibited a statistically significant reduction ($P<0.05$) in the number of implantation sites compared with the control group (Table 2). The study found that maternal exposure to paracetamol substantially impacted fetals' weights, resulting in their reduction when compared with the control group. The concurrent administration of paracetamol+curcumin demonstrated a statistically significant rise ($P<0.05$) compared with the group receiving only paracetamol, as well as a statistically significant decrease ($P<0.05$) compared with the control group. The fetus length in the three experimental groups exhibited a statistically significant decrease ($P<0.05$) compared with the control group (Table 2).

Table 1: Effect of paracetamol and/or curcumin on the body weight gain, uterus weight, and placenta weight (g) of pregnant rats at the 20th day of gestation.

	Body weight gain (g)	Uterus weight (g)	Placenta weight (g)
Control	45.2±5.7	37.3±4.2	0.52±0.01
Curcumin	39.9±1.7 P_a=0.65	36.6±1.5 P_a=1.00	0.53±0.01 P_a=0.95
Paracetamol	10.3±1.64* P_a=0.00	33.7±1.3 P_a=0.70	0.48±0.01 P_a=0.41
Paracetamol+ Curcumin	19.1±1.6* P_a=0.00 P_b=0.25	35.6±0.7 P_a=0.96 P_b=0.94	0.54±0.03 P_a=0.85 P_b=0.09

P_a: probability relative to the control group, P_b: probability relative to the paracetamol group, *: significant ($P<0.05$) relative to the control group.

Table 2: Effect of paracetamol and/or curcumin on pregnancy outcome at the 20th day of gestation.

	Number of implantation sites	Fetal weight	Fetal length
Control	9.17±0.31	3.03±0.11	3.60±0.06
Curcumin	8.50±0.22 P_a=0.32	2.75±0.03 P_a=0.07	3.20±0.09* P_a=0.00
Paracetamol	6.83±0.31* P_a=0.00	1.99±0.05* P_a=0.00	3.00±0.04* P_a=0.00
Paracetamol+ Curcumin	7.33±0.21* P_a=0.00 P_b=0.56	2.42±0.06*# P_a=0.00 P_b=0.001	3.21±0.06* P_a=0.00 P_b=0.11

P_a: probability relative to the control group, P_b: probability relative to the paracetamol group, *: significant ($P<0.05$) relative to the control group, #: significant ($P<0.05$) relative to the paracetamol group. The postimplantation loss index (%) in all groups = 0.

Effect of curcumin and paracetamol on the skeletal status of rats' fetuses

The axial skeleton (consisting of the skull, vertebrae, and ribs) along with the appendicular skeleton (which encompasses the fore and hind limbs, as well as pectoral and pelvic girdles) were undergo ossification by the 20th day of gestation, as observed in cleared cartilage and bone preparations of the control rats' fetuses (Figure 1). Based on the comparative analysis, no discernible variations in ossification were observed among all groups.

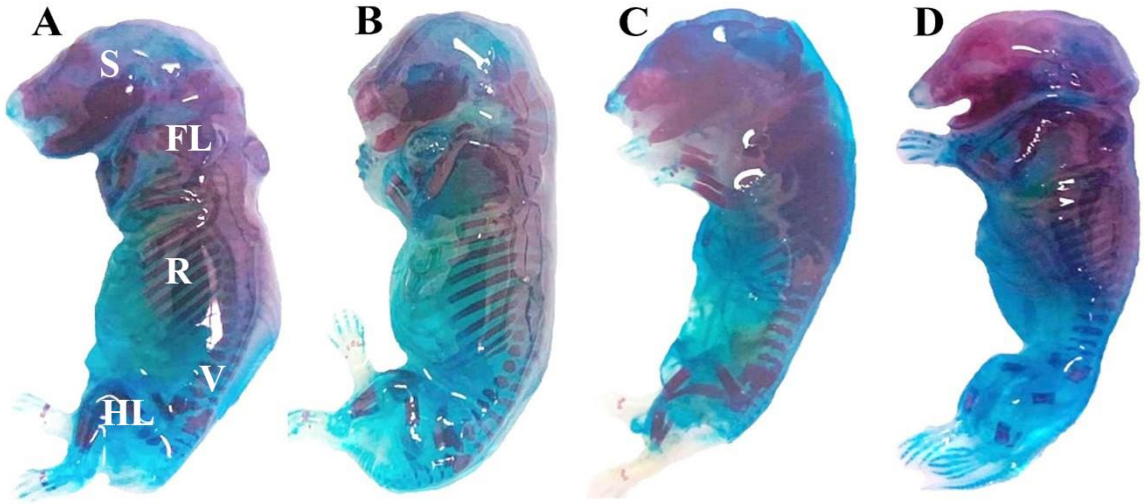

Figure 1: Photographs of the fetal skeleton on the 20th day of gestation stained with the Alcian blue-Alizarin red double staining method. **(A)** Control group, **(B)** curcumin-treated group, (C) paracetamol-treated group, **(D)** paracetamol+curcumin-treated group. Skull (S), fore limb (FL), ribs (R), vertebrates (V) and hind limb (HL).

Effect of curcumin and paracetamol on the hepatic oxidative stress/antioxidant markers in maternal and fetal rats

The concentration of MDA in the maternal group administered with paracetamol exhibited a statistically significant elevation (P<0.05) in comparison with the control group. However, the concurrent administration of paracetamol+curcumin demonstrated a statistically significant reduction (P<0.05) in the MDA level compared with the group receiving only paracetamol (Table 3). Compared with the control group, the hepatic tissue of pregnant rats that received paracetamol treatment exhibited a significant reduction (P<0.05) in GSH level and SOD activity. In contrast, the decline in CAT activity was not statistically significant (P≥0.05). The experimental group that received a combination of paracetamol+ curcumin demonstrated a statistically significant decrease (P<0.05) in GSH level, but not in the activities of SOD and CAT, compared with the control group (Table 3).

In contrast to the control group, the hepatic tissue of fetuses subjected to paracetamol treatment exhibited statistically significant increases (P<0.05) in the concentrations of MDA, and the activities of SOD and CAT, as well as a statistically significant decrease (P<0.05) in levels of GSH (Table 4). The simultaneous administration of paracetamol+curcumin resulted in an insignificant rise in GSH level (P≥0.05) and substantial reductions (P<0.05) in MDA level, as well as SOD and CAT activities, in the hepatic tissue of fetuses compared with the group that only received paracetamol. Additionally, there were insignificant differences (P≥0.05) in MDA level, as well as SOD and CAT activities, and significant decrease (P<0.05) in GSH level in paracetamol+curcumin-treated groups compared with the control group (Table 4).

Table 3: Effect of curcumin and/or paracetamol on the oxidative/antioxidant status of maternal liver.

	MDA (nmol/g tissue)	GSH (mg/g tissue)	SOD (U/g tissue)	CAT (U/g tissue)
Control	6.4 ±0.7	1.19±0.06	83.8±1.1	26.2±1.3
Curcumin	4.1± 0.5 P_a=0.23	0.98±0.02 P_a=0.12	78.4±3.5 P_a=0.59	28.3±0.9 P_a=0.56
Paracetamol	15.6±1.1* P_a=0.00	0.46±0.05* P_a=0.00	70.0±3.9* P_a=0.04	23.4±1.3 P_a=0.32
Paracetamol+ Curcumin	7.2± 0.9$^{\#}$ P_a=0.93 P_b=0.00	0.68±0.07* P_a=0.002 P_b=0.08	75.8±2.5 P_a=0.29 P_b=0.54	25.4±0.8 P_a=0.94 P_b=0.59

MDA: malondialdehyde, GSH: reduced glutathione, SOD: superoxide dismutase, CAT: catalase. P_a: probability relative to the control group, P_b: probability relative to the paracetamol group, *: significant (P<0.05) relative to the control group, $^{\#}$: significant (P<0.05) relative to the paracetamol group.

Table 4: Effect of curcumin and/or paracetamol on the oxidative/antioxidant status of fetal liver.

	MDA (nmol/g tissue)	GSH (mg/g tissue)	SOD (U/g tissue)	CAT (U/g tissue)
Control	3.2±0.3	6.7±0.1	271.7 20.4	154.8±6.8
Curcumin	3.1±0.5 P_a=0.99	4.2±0.8 P_a=0.14	296.3±74.8 P_a=0.97	147.0±6.12 P_a=0.98
Paracetamol	14.9±0.9* P_a=0.00	2.2± 0.8* P_a=0.01	538.5±8.5* P_a=0.007	253.0±27.5* P_a=0.006
Paracetamol+ Curcumin	3.7±0.3$^{\#}$ P_a=0.91 P_b=0.00	3.8± 0.9* P_a=0.08 P_b=0.45	355.8±17.8$^{\#}$ P_a=0.49 P_b=0.04	178.8±2.8$^{\#}$ P_a=0.66 P_b=0.03

MDA: malondialdehyde, GSH: reduced glutathione, SOD: superoxide dismutase, CAT: catalase. P_a: probability relative to the control group, P_b: probability relative to the paracetamol group, *: significant (P<0.05) relative to the control group, $^{\#}$: significant (P<0.05) relative to the paracetamol group.

Effect of curcumin and paracetamol on the histological alterations in liver of maternal and fetal rats

Maternal liver sections of control and curcumin groups exhibited the regular appearance of the central vein with the normal lining of the endothelium (Figure 2A,C) and a typical portal vein (Figure 2B,D) with hepatic artery and bile duct. In addition, regular hepatic cords emerged, homing polygonal hepatocytes with large, round central light, vesicular nuclei. Hepatic sinusoids separate these cords along with Kupffer cells. In the paracetamol group (Figure 2E,F), the central vein area existed with slight congestion and detachment in the lining endothelium, and the portal area revealed obvious epithelial desquamation and sub-epithelial inflammatory cell infiltrations. Severe hepatic tissue degeneration is emphasized in both areas, such as fatty steatosis and ballooning, pyknotic hepatocytes, dilatation of hepatic sinusoids, and dispersed necrotic areas. These histopatho-

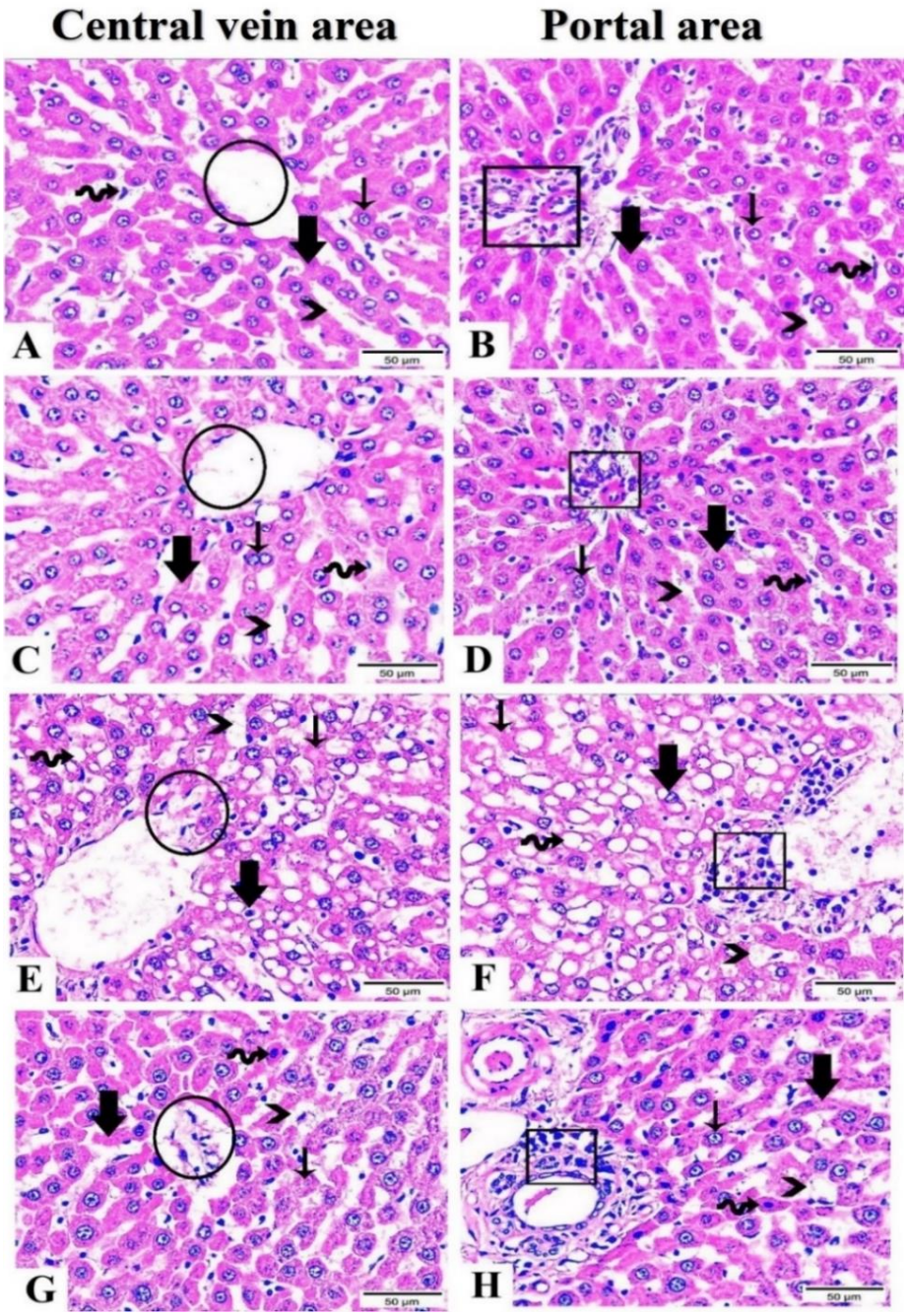

Figure 2: Photomicrographs displayed the histopathological alterations in liver tissues of pregnant rats between studied groups (hematoxylin and eosin staining, magnification: 400×, scale bar: 50 μm). The control group **(A** and **B)**; the curcumin group **(C** and **D)**, circle: central vein area with standard lining endothelium, cube: hepatic artery and bile duct, thick arrows: regular hepatic cords, thin arrow: hepatocytes with vesicular nucleus, arrowheads: sinusoids, wave arrows: Kupffer cells; the paracetamol group **(E** and **F)**, circle: slight congestion and detachment in the lining endothelium, cube: epithelial desquamation and sub-epithelial inflammatory cells infiltrations, wave arrows: fatty steatosis and ballooning, thick arrows: pyknotic hepatocytes, arrowheads: dilatation of hepatic sinusoids, thin arrows: dispersed necrotic areas; the paracetamol+curcumin group **(G and H)**, circle: traces of desquamated epithelium of central vein and few aggregated inflammatory cells, cube: low inflammatory cells infiltrations in portal area, thick arrow: hepatic cords, arrowheads: dilated sinusoids with detached epithelial lining, wave arrows: apoptotic hepatocytes, thin arrows: normal hepatocyte.

logical changes induced by paracetamol were prohibited by co-treatment with curcumin, with notable ameliorative effects (Figure 2G,H). In the curcumin-paracetamol treatment group (Figure 2G,H), the central vein posed a desquamated epithelium in line with a few aggregated inflammatory cells. Portal area was marked with moderate inflammatory cell infiltrations with intact lining epithelium. Hepatic tissue highlighted with great structure improvement with obvious reduction in liver steatosis, regular hepatic cords, and dilated sinusoids with detached epithelial lining. Besides, hepatocytes were observed in apoptotic and light vesicular (Figure 2G,H). Compared with the control group, paracetamol administration significantly elevated (P<0.05) the number of inflammatory cells and degenerated hepatocytes, as well as the area percentage of congestion and hemorrhage (Table 5). However, paracetamol+curcumin significantly decreased (P<0.05) these parameters compared with the paracetamol group (Table 5).

Table 5: Effect of curcumin and/or paracetamol on the maternal and fetal hepatic histopathological scoring.

	Number of hepatocytes exhibited degeneration		Number of inflammatory cells		Area percentage of hemorrhage and congestion	
	Mother	Fetus	Mother	Fetus	Mother	Fetus
Control	7.0±0.6	4.3±0.9	4.7±0.9	6.7±2.2	1.6±0.4	0.51±0.07
Curcumin	9.3±0.9 P_a=0.94	5.3±1.5 P_a=0.99	7.0±1.2 P_a=0.93	10.0±1.5 P_a=0.8	1.9± 0.4 P_a=1.00	0.25±0.05* P_a=0.99
Paracetamol	81.7±5.0* P_a=0.00	65.7±3.5* P_a=0.00	73.6±4.8* P_a=0.00	84.0±0.0* P_a=0.00	37.5± 3.2* P_a=0.00	26.6±0.83* P_a=0.00
Paracetamol+ Curcumin	51.3±2.6*# P_a=0.00 P_b=0.00	31.6 ±1.8*# P_a=0.00 P_b=0.00	22.0±2.1*# P_a=0.01 P_b=0.00	21.7±1.8*# P_a=0.01 P_b=0.00	11.8±0.8*# P_a=0.01 P_b=0.00	8.22±1.01*# P_a=0.00 P_b=0.00

P_a: probability relative to the control group, P_b: probability relative to the paracetamol group, *: significant (P<0.05) relative to the control group, #: significant (P<0.05) relative to the paracetamol group.

Fetal liver inspection of control (Figure 3A,B) and curcumin groups (Figure 3C,D) exhibited central vein area disclosed regular lining endothelium and portal area indicated with its portal vein and less differentiated hepatic artery and bile duct components. In both areas, sheets of polygonal hepatocytes were developed with large, round central light vesicular nuclei separated by hepatic sinusoids. Various stages of erythroblast dispersed encircling hepatocytes and multinucleated megakaryocytes were noticed. In the paracetamol-treated group (Figure 3E,F), the central vein exhibited congestion and limited areas with degenerated epithelium, and the portal area revealed congestion, inflammation, and deteriorated lining epithelium of the portal vein. In the paracetamol+curcumin group (Figure 3G,H), the hepatic tissue emphasized enhancement in tissue structure as hepatocytes were detected as light vesicular form except for a few apoptotic ones, and dilated hepatic sinusoids were also observed. However, the central vein emerged with degenerated lining endothelium and portal area exposed epithelial desquamation and few sub-epithelial inflammatory cell infiltrations. The administration of paracetamol resulted in a notable increase (P<0.05) in the quantities of inflammatory cells, deteriorated hepatocytes, and the percentage of congestion and bleeding observed in the affected area compared with the control group. However, the combination of paracetamol+curcumin showed a significant decrease in these parameters compared with the paracetamol group (Table 5).

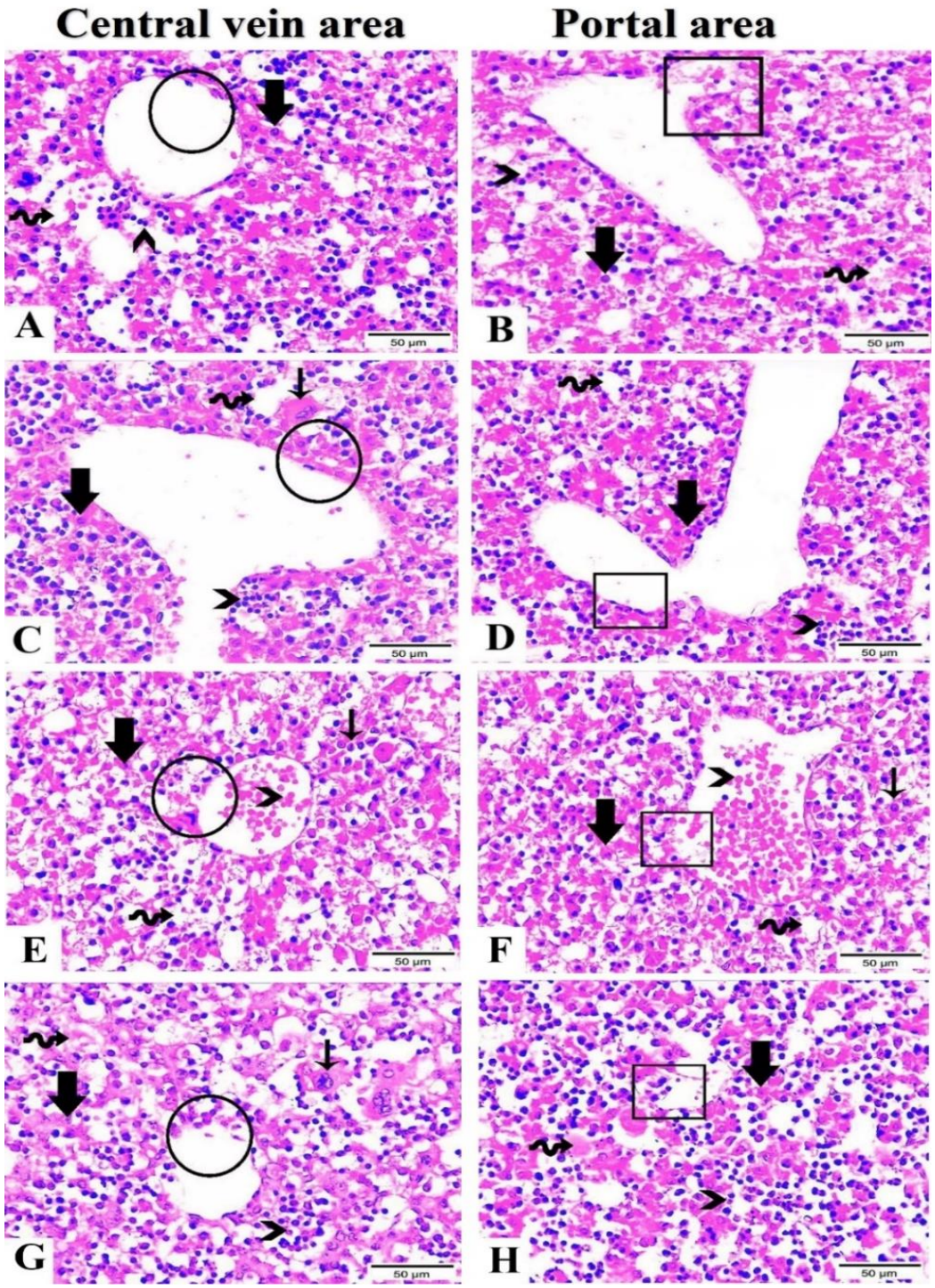

Figure 3: Photomicrographs presented the histopathological variations in liver tissues of fetus rats among examined groups (hematoxylin and eosin staining, magnification: 400×, scale bar: 50 µm). The control group **(A** and **B)**; the curcumin group **(C** and **D)**, circle: central vein with regular endothelium, cube: hepatic artery and bile duct, thick arrows: hepatocytes, wave arrows: sinusoids, arrowheads: erythroblast, thin arrows: multinucleated megakaryocyte; the paracetamol group **(E** and **F)**, arrowhead: congestion of central vein, circle: degenerated epithelium, arrowhead: congestion of portal vein, cube: inflammation and degenerated epithelium, thin arrows: normal hepatocytes, thick arrows: apoptotic cells, wave arrows: sinusoids; the paracetamol+curcumin group **(G and H)**, circle: central vein, cube: inflammatory cell infiltrations, thick arrows: pyknosis, arrowheads: erythroblast cells, thin arrow: multinucleated megakaryocyte, wave arrows: necrosis.

DISCUSSION

The administration of paracetamol to rats resulted in a significant decrease in body weight gain compared with the control group. Nevertheless, the uterus and placenta weights in all treatment groups did not exhibit a statistically significant reduction compared with the control group. Burdan (2003) reported a notable reduction in maternal weight growth among pregnant rats subjected to paracetamol and caffeine treatment[23]. Contrary to prior findings, the mothers who received paracetamol and their female progeny did not indicate weight increase or decrease[18]. The observations above support previous studies that have demonstrated that maternal administration of paracetamol at the same dosage between gestational periods (days 13.5-17.5 or days 6-21) did not result in any alterations in the body weight of both the maternal dams and their offspring[24,25]. Furthermore, the findings shown by Klein *et al*.[25] underscored the absence of any maternal body weight alteration following paracetamol administration. Paracetamol exhibits an extended half-life and minimizes the removal rate in pregnant rats relative to nonpregnant rats. In addition, it has been observed that administering 300 mg/kg of paracetamol intravenously during pregnancy leads to alterations in its elimination and biotransformation pathways[26]. The group administered with paracetamol exhibited a notable reduction in fetal weight and length compared with the control group. There was a notable disparity in fetal body length among the pregnant rats subjected to a dosage of 350 mg/kg of paracetamol, as observed in the study conducted by Burdan *et al*.[27]. However, it should be noted that no statistically significant disparity was observed in the fetal body weight of offspring who were administered paracetamol during pregnancy compared with the control group, as reported by Dean *et al*.[28] and Kelin *et al*.[25].

Based on the analysis of skeletal examination in comparison with the control group, no significant variation in ossification was observed among the three treated groups, indicating normal ossification. This finding is consistent with previous studies that have revealed no significant increase in skeletal deformities associated with the use of paracetamol. These studies have also indicated that paracetamol is generally well tolerated by both the fetus and the mother[29].

The relationship between cellular oxidative stress and liver injury in situations of acute paracetamol overdose has been frequently seen[30]. According to Hinson *et al.*[31], the substance undergoes a transformation process, forming a potent hepatotoxic compound. This compound induces liver necrosis, leading to fatality in experimental animals. The findings of our study indicate a considerable increase in maternal and fetal hepatic MDA levels compared with the control group. The measurement of MDA is commonly regarded as a significant biomarker for assessing oxidative stress and lipid peroxidation that induced tissue damage[32].

Curcumin is a naturally existing phenolic chemical derived from the yellow-pigmented segment of the turmeric plant. The subject in question received considerable interest mainly due to its wide range of biological effects including antioxidant properties[33]. The potential effects of curcumin appear to show promise in reducing the negative impacts induced by chemically hazardous agents in pregnant individuals. The administration of curcumin to maternal subjects resulted in an augmentation of glutathione peroxidase activity and an expansion of the blood sinusoid area within the placenta[34]. Moreover, the administration of curcumin supplements led to a decrease in MDA content and the occurrence of apoptosis within the placenta. The combined impact of these factors resulted in an enhancement of placental efficiency[34].

The histological analysis of rats treated with paracetamol demonstrated significant degradation of hepatic tissue, as evidenced by the presence of pyknotic hepatocytes, steatosis, and necrotic areas throughout the liver. Exposure to paracetamol can lead to

notable degeneration, necrosis, steatosis, and infiltration of inflammatory cells[35]. These effects are induced through the production of harmful reactive metabolites, particularly N-acetyl benzoquinone imine (NAPQI). The hepatotoxicity observed in paracetamol-induced liver injury is mostly attributed to NAPQI, which leads to a depletion of glutathione levels[35]. Consequently, an overdose of paracetamol can result in a substantial deficiency of liver GSH, leading to serious liver cell necrosis, acute liver failure, or potentially fatal outcomes[36]. The present investigation observed a decline in the quantity of GSH in the hepatic tissue of both dams and fetuses. Simultaneously, SOD and CAT activities exhibited a drop in the maternal liver, while experiencing an enormous rise in the fetal liver. Based on the findings of Hussain *et al*.[37], it was observed that the group treated with paracetamol had heightened levels of lipid peroxidation and reduced enzymatic activity, namely in the case of SOD, GSH, CAT, glutathione reductase, and glutathione peroxidase in rat uterus. Previous research has also demonstrated a reduction in hepatic antioxidant markers after administering paracetamol in pregnant rats, with a particular focus on the activity of SOD[38].

The nuclear factor erythroid 2-related factor 2 (NRF2) protein is a transcription factor that resembles a zipper, with a predominant composition of leucine residues. The primary role of this mechanism is to protect cells from oxidative stress and apoptotic damage by regulating antioxidant enzyme production[39]. Previous study have demonstrated that curcumin can alleviate hepatic oxidative stress by activating the NRF2 pathway. The hepatic expression of NRF2 is found to be downregulated in the liver of rats exhibiting intrauterine growth retardation[40]. The research conducted by Yousef *et al*.[41] provided empirical evidence supporting the hepatoprotective properties of curcumin in ameliorating liver necrosis induced by paracetamol. Moreover, curcumin exhibits anti-inflammatory properties by suppressing the synthesis of cyclo-oxygenase-2 and inducible nitric oxide synthase, in addition to decreasing the expression of tumor necrosis factor-alpha through the inhibition of nuclear factor kappa-B activation[42]. Hence, the documented beneficial impact of curcumin can be attributed to its intrinsic antioxidant and anti-inflammatory characteristics[43].

In summary, the findings of this study indicated that paracetamol has teratogenic properties, leading to histological alterations in the liver of both maternal subjects and their offspring. Additionally, paracetamol administration was found to produce oxidative stress. The results of this study suggest that the administration of curcumin to pregnant rats may potentially mitigate the effects of paracetamol

AUTHOR'S CONTRIBUTIONS

ARO and HAA conceived and designed research. ARO, HAA, and DMA conducted experiments. ARO performed the statistical analysis. ARO, HAA, and DMA summarized, discussed, and interpreted the results. All authors drafted the manuscript and approved the manuscript.

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CONFLICT OF INTEREST

The authors declare no competing interests.

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تقييم التأثير المحتمل للكركمين و/أو الباراسيتامول في جِرذان ويستار الحوامل وأجنتها

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تهدف الدراسة الحالية إلى تقييم التأثيرات المحتملة للكركمين و/أو الباراسيتامول على أمهات جِرذان ويستار (*Rattus norvegicus*) وأجنتها في أثناء الحمل. تم توزيع الإناث الحوامل إلى أربع مجموعات (6 جِرذ/لكل مجموعة). تلقت المجموعة الضابطة المزيب يوميًا/عن طريق الفم، ومجموعة الكركمين (15.75 ملجم/ كجم من وزن الجسم)، ومجموعة الباراسيتامول (350 ملجم/كجم من وزن الجسم)، وتلقت المجموعة المشتركة الباراسيتامول والكركمين في وقت واحد، وذلك في أثناء فترة الحمل (اليوم السادس إلى اليوم التاسع عشر). وتم في هذه الدراسة قياس معايير نتائج الحمل، وحالة الهيكل العظمي للجنين، والإجهاد التأكسدي الكبدي، والتغيرات النسيجية. كشفت النتائج الحالية عن العواقب غير الآمنة للباراسيتامول على الحمل. وفي الوقت نفسه، تسبب الباراسيتامول في تأخر نمو الجنين، وتغيرات كبدية نسيجية، وتغيير ملحوظ إحصائيا ($P<0.05$) في الأكسدة الكبدية للأم والجنين. لم يؤثر تناول الباراسيتامول على تعظم العظام الهيكلية. على العكس من ذلك، أدت المعاملة بالكركمين يوميًا إلى تحفيف التأثير السلبي للباراسيتامول وتحسين معايير نمو الجنين، واستعادة الأنسجة الكبدية الطبيعية، وانخفاض مستويات تأكسد الدهون، وزيادة مضادات الأكسدة في أنسجة الكبد للأمهات وأجنتها. في الختام، قد يكون الكركمين عامل وقائي يعكس التأثير السام للباراسيتامول أثناء الحمل. وسيتم إجراء المزيد من الدراسات لتوضيح الآليات والمسارات الدقيقة التي يمكن للكركمين من خلالها تخفيف التأثير الضار للباراسيتامول.